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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,321	04/13/2001	Jeffrey V. Ravetch	TRU-0005	2584

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/834,321	RAVETCH, JEFFREY V.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,10-13,15 and 23-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 10-13, 15 and 23-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/05/06 has been entered.

2. Claims 1, 10-13, 15 and 23-43 are pending and under consideration in the instant application.

In view of the amendment, filed 12/05/06, the following rejections remain:

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 10-13, 15 and 23-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention for the same reasons set forth in the previous Office Action, mailed 06/02/06.

Applicant's arguments, filed 12/05/06 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) The Specification clearly states that the broader invention is an antibody with reduced binding to FcRiiB without limitation that it must retain binding to FcRiiA and FcRIII A; (ii) Only in one specific embodiment the specification disclosed that "it is preferred that antibody retaining or enhancing binding to FcRIIA or FcRIIIA." The Specification never disclosed that "it is essential that antibody retained or enhancing binding to FcRIIA or FcRIIIA" to practice the invention.; (iii) The absence of working examples is not enough evidence that the present application is not enabled; (iv) The present application clearly teaches and enables one skill in the art to make an antibody that reduced binding to the FcRIIB

receptor, as evidence from Declaration under C.F.R 1.132 by Dr. Ravetch; (v) Pears et al. reference does not state that the claimed invention is unpredictable.
Contrary to Applicant's assertion the issue raised in the previous Office Action was not about the ability one skill in the art to make antibody with reduce affinity to FcRIIB. The Examiner acknowledge that, as evidence from Declaration under C.F.R 1.132 by Dr. Ravetch and accompanied Shield reference, its only required routine experimentation.

However, the issue raised in the previous Office Action was that in the absence of working example ; art recognized correlation between reducing the binding affinity of therapeutic antibody to FcRIIB and enhancing cytotoxicity elicited by said antibody, absent the ability to predict which of these antibodies would function as claimed, and given the lack of data on regions critical for said activity, one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

With regard to the issue that " only in one specific embodiment the specification disclosed that it is preferred that antibody retaining or enhancing binding to FcRIIA or FcRIIIA." The Specification never disclosed that "it is essential that antibody retained or enhancing binding to FcRIIA or FcRIIIA" to practice the invention.

After carefully reading the Specification, it is the Examiner understanding that to practice the claimed invention, the antibody has to retain or enhanced binding to FcRIIA and FcRIIIa (see page 7 in particular). Moreover, in the example disclosed in the Specification, it is specifically stated that anti-tumor activity of modified very specific antibody, i.e. 4D5, Herceptin^{R} and Rituxan ^{R} each require the binding to activation receptor . i.e. to FcRIIA and FcRIIIa (see ovedrlapping pages 33 and 34 in particular). Since there is no any working examples in the Specification to shows that by only reducing the binding affinity of therapeutic antibody to FcRIIB it is possible to enhance cytotoxicity of said antibody, an undue experimentation would be required to determine which modifications would be acceptable to retain occluding structural and functional activity as required to practice the invention.

It is also noted, that the reference submitted by Dr. Ravetch in his CFR 1.132 Declaration further supported the Examiner position. In said reference, Shields et al., explicitly teach that " given the possible involvement of FcR in mechanism of action of therapeutic antibodies, human IgG1 variants with **improved binding capacity to human FcR, especially variants with better binding to Fc RIIIA** and simultaneously abrogation of binding to the inhibitory Fc RIIB could be used to provide more efficacious therapeutic antibody" (emphases added) . In other words , even the reference provided by Applicant, teaches that therapeutic antibody should retain or improve its binding to activating Fc receptor, i.e. to FCRIIA and Fc RIII A.

A description of a protein by functional language in the absence of a structure is not considered sufficient to show possession of the claimed invention. See Fiers, 984 F.2d at 1169-71, 25 USPQ2D at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many species may achieve that result. The definition requirement of the

patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 /f.2d 1516, 1521, 22 USPQ 369, 372-73 (Fed. Cir. 1984) affirming the rejection because the specification does "little more than outline[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what the material consists of (e.g. structural feature), is not a description of that material.

Since the instant fact pattern fails to indicate that representative number of structurally related compounds, i.e. the genus of antibodies that have a reduced binding affinity for FcRIIB , due to modification of the Fc portion of the antibody , that can be use in a method of enhancing cytotoxicity, the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claims and consequently would not know how to make them. An assay for *finding* a product is not equivalent to a positive recitation of *how to make* a product.

With regards to Applicants comments that Pears et al. reference does not state that the claimed invention is unpredictable.

The issue raised in the Previous Office Action was that in the absence of working example to show the effectiveness of the method of enhancing cytotoxicity , which method comprises disrupting activation of SHIP by Fc RIIB , wherein said disruption is accomplished by inhibiting binding of said antibody to FcRIIB, and based only on Example 1, wherein FcγRIIB deficient mice, i.e. mice lacking FcγRIIB was used, it is unpredicted how to correlate said limited data with *in vivo* therapeutic treatment in any mammalian including human, commensurate in scope with the claimed invention. The Pearse et al., reference was used to show that at the time the invention was made, one skill in the art would know that interpretation of data obtained on mice deficient in FcγRIIB is complicated, since animals deficient in the inhibitory receptors have different responses compare to control ones.

It is the examiner position that the specification does not provide sufficient guidance and examples as to which modifications would be acceptable to retain these specific structural and functional properties of claimed antibodies to be used in the claimed method for enhancing cytotoxicity elicited by antibody *in vivo,* which method comprises disrupting activation of SHIP by FcRIIB. In addition, the term "modifying" encompass any substitution, deletion or insertion (page 14, lines 13-16 of Specification as filed) of Fc portion of the antibody that will affect their structural and functional properties. Applicant acknowledges that single amino acid replacement in Fc portion of the mouse anti-HER2 antibody 4D5 reduces affinity for **both** FcRII and FcRIII receptors (page 35, lines 5-20 of the Specification as filed). The references cited by the examiner indicated that protein chemistry is probably one of the most unpredictable areas of biotechnology and that it is known in the art that even single amino acid changes or differences in a proteins amino acid sequence can have dramatic effects on the protein's function.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method for enhancing cytotoxicity elicited by a therapeutic antibody *in vivo*, which method comprises disrupting activation of SHIP by Fc RIIB in manner reasonably correlated with the scope of the claims. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, lack of working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

5. No claim is allowed

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MICHAIL BELYAVSKYI, PH.D.
PATENT EXAMINER

2/2/07